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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,780	02/20/2004	Asa Abeliovich	5199-70	6675

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,780	ABELIOVICH ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 24-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 06/02/06 has been acknowledged.

Election/Restrictions

Applicant's election with traverse of Group III claim 20 in the reply filed on 06/02/06 is acknowledged. The traversal is on the ground(s) that Claim 21-23 should be examined with the elected group III. This is found persuasive, therefore claims 20-23 are included and are examined as Group III.

Claims 1-19 and 24-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/02/06.

Claims 20-23 are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses a nucleic acid encoding a parkin-associated agent selected from group consisting of consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity, wherein the nucleic acid is of any natural or non-natural origin. At the best the specification teaches cDNA encoding parkin protein. Besides cDNA encoding human parkin protein, the specification as filed fails to disclose a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity derived from any non-natural (genetically modified) and natural (derived from any organism) origin.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e conserve motifs or domains).

The specification fails to disclose representative number of species by structure and function encompassed by genus as claimed. Furthermore the genus as claimed encompasses structurally and functionally distinct members. Claiming all divergent species that achieve a result as contemplated by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the

information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)." To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish

genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406)*. In the instant case the nucleic acid sequences as claimed has been defined only by a statement of function that broadly encompasses a "parkin-associated agent" which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a lentiviral vector encoding human parkin protein, does not reasonably provide enablement for any other composition comprising a lentiviral vector encoding a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity, wherein the nucleic acid is of any natural or non-natural origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Since the specification fails to disclose a representative number of species defined by structure and function, it is unclear how one skilled in the art use the invention as claimed (supra). The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all parkin-associated agents selected from a group consisting of a parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity, wherein the nucleic acid is of any natural or non-natural origin. At issue, under the enablement

requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claims 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention

The invention of instant claim relates to a method for treating a neurodegenerative diseases via method for gene therapy.

Breadth Of Claims And Guidance Provided in the Specification

The scope of invention as claimed encompasses the treatment of any neurodegenerative diseases especially sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease by administering a lentiviral vector encoding any parkin-associated agent, wherein the lentiviral vector is administered to the subject via any and all routes of administration.

State Of Art And Predictability

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Goncalves, Bioessays. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end

points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case the scope of invention as claimed encompasses the treatment of any neurodegenerative diseases especially sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease by administering a lentiviral vector encoding any parkin-associated agent, wherein the vector is administered to the subject via any and all routes of administration. The specification as filed fails to disclose that the administration of a lentiviral vector encoding any parkin associated agent like parkin protein, a parkin mimetic, a modulator of parkin expression, and a modulator of parkin activity, wherein the agent is of any natural or non-natural origin result in the treatment of any neurodegenerative diseases as broadly claimed herein. The specification even fails to provide an enabling disclosure that would enable one skilled in the art to treat sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease by administering a lentiviral vector encoding the parkin protein. At best the specification provides in-vitro transformation of isolated neuronal cells, which does not recapitulate the complex ties involved in a method associated with gene therapy.

Furthermore the etiology of Parkinson's disease (PD) is multifactorial and complex (see Abliovivh et al J. Neurochem10.111/j.1471-459, 2006.04102.x. Multifactorial, also called complex or common diseases, provide challenging problems for geneticists because most cases are believed to result from the combined action of multiple genes and environmental factors such as diet, toxins and exposure to drugs. Hence very often these diseases show a complex pattern of inheritance. Many of the genes involved in these types of disorders may not have a significant or additive effect in causing disease. The causes of PD are unknown but considerable evidence suggests a multifactorial etiology involving genetic and environmental factors. PD is a slowly progressive, neurodegenerative disorder characterized by the irreversible loss of over

80% of the nigrostriatal dopaminergic neurons. Although the pathogenesis of the disease appears to be multifactorial, correlative evidence supports the role of oxidative stress and mitochondrial dysfunction. PD patients have reduced levels of mitochondrial complex I and glutathione activity, as well as increased levels of superoxide dismutase activity, lipid peroxidation and iron in the substantia nigra. This evidence suggests that the generation of reactive oxygen species (ROS), such as the superoxide ion and hydrogen peroxide, plays a significant role in dopamine (DA) neuronal death. Despite decades of research, the primary insults and mechanisms leading to the degeneration of the nigrostriatal DA neurons and the increase in production of ROS in PD is unknown. Nonhuman primates do not naturally develop PD, so these model systems are unavailable to study the etiology of the disease. Current animal and tissue culture systems are able to mimic some of the pathology and morphology of idiopathic PD. However, identifying the molecular determinants involved in PD without any a priori knowledge of the mechanism of the neurodegeneration is significantly hindered due to the lack of a definitive model system. In additon, if PD in humans is a multifactorial disease, controlled delivery and expression of a gene even by using an inducible and a safe vector, may only provide partial benefit for the patient. Because typical PD is likely to be determined by environmental factors, and age is a consistent risk factor, it is necessary to understand first what factors are responsible in an age dependent manner for the selective loss of nigrostriatal neurons before an efficient strategy for its prevention can be undertaken (see Nass et al, Parkinsonism Relat Disord. (3):185-191. 2001; Shastry Neuroscience Research 41:5-12, 2001).

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is

much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Furthermore, inserting genes may affect other areas of a host's biology may be even more complex when genes are introduced into the brain as opposed to other organ systems. Only so much can be learned from animal models, researchers point out, and the effect on things like language, which is unique to humans, can be evaluated only in human trials. Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

In instant case treatment of any neurodegenerative disease especially sporadic Parkinson's disease or autosomal recessive early-onset Parkinson's disease by administering a lentiviral vector encoding any "parkin-associated agent" is not considered routine in the art and without sufficient guidance to the treatment resulted from a specific therapeutic parkin-associated agent the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: a lentiviral vector encoding a nucleic acid sequence encoding a parkin-associated agent.

Claim 23 provides for the use of a therapeutic composition of claim 20, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 23 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 20 is rejected under 35 U.S.C. 102(a) as being anticipated by Bianco et al PNAS 99(16):10813-10818, 2002). The scope of instant claim encompasses a lentiviral vector encoding the parkin-associated agent. The cited art teaches a lentiviral vector encoding the α-synclein protein (see page10814, colo.1 para. 2). Thus given the broadest reasonable interpretation the cited art clearly anticipate the invention as claimed.

Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by Kingsman (US 2003/0180740 A1 2003). The scope of instant claim encompasses a lentiviral vector encoding the parkin protein. The cited art teaches a lentiviral vector encoding the parkin protein (see page 42-43). Thus the cited art clearly anticipate the invention as claimed.

Specification (Notice To Comply)

With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:
(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application (see MPEP 2422.03).

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

The instant specification fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures because: *The specification fail to provide SEQ ID NO(s) for the nucleotide sequences disclosed on pages 45 and Fig-13.*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

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